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THE ANTIMONY TRICHLORIDE METHOD FOR THE DETERMINATION OF VITAMIN A[1]

By G. H. Benham[2]

Abstract

A critical description of the antimony trichloride method for the determination of vitamin A is presented. Low values for vitamin A result from:

(1) Incomplete extraction from the alcoholic soap solution by using petroleum ether instead of ethyl ether,

(2) Incomplete separation of the layers during extraction and washing,

(3) Incomplete filtration through anhydrous sodium sulphate.

If strict attention is paid to details of procedure, the method gives consistent and reproducible results. Uncertainty in regard to the exact factor for converting the *E* values to international units makes it impossible at this time to state accurately the absolute values. It is pointed out that this in no way detracts from the usefulness of the chemical test.

Introduction

It is conceded that the physiological approach to vitamin A determinations is by biological assay. It is nevertheless of great importance to the chemist to have at hand reliable chemical methods whereby vitamin concentrations may be determined, inasmuch as many laboratories have neither the facilities nor the time for biological assay.

The development of the chemical method involving the use of antimony trichloride ($SbCl_3$), whereby a blue colour is formed, has been accompanied by many difficulties. Views have clashed as to its value in terms of true biological vitamin content, and as to its accuracy *per se.*

The early work showed great variability between results obtained with the same sample of oil by different workers in the same laboratory and by workers in different laboratories (Evers (15)). It was stated that the blue colour produced by an oil with antimony trichloride was not proportional to the amount of oil used, except at very low concentrations (Norris and Danielson (37)). Ender (14) showed that the complicated behaviour of the vitamin was due to the fact that there were two chromogens, one of which was possibly identical with vitamin A, the other having no connection with growth but still giving a blue colour with antimony trichloride. Levine and Richman (26)

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maintained that the test was not specific for vitamin A, since many other sterols and pigments were similarly chromogenic. Drummond and Morton (8), however, using the spectroscopic method, which had just been developed, stated that there was good agreement between values obtained with this method and the blue values obtained with the antimony trichloride method, using the tintometer for colour matching.

These conflicting statements have led to confusion as to the suitability of the antimony trichloride method, especially as a number of workers have reported satisfactory correlation between values obtained by biological assay and the blue values (Coward *et al.* (4), Lathbury (25)).

In 1934, Bacharach and Smith (2) presented a full discussion of the antimony trichloride method, and stated that:

> "the intensity of the blue colour is not proportional to the concentration with low values because of the presence of inhibiting substances. In rich sources there are less of these, so that the blue colour is more nearly linear."

Attention was then focused on these inhibiting substances present in oils and concentrates (to a larger extent in plant material than in liver oils) (Wokes and Willimott (47)). According to With (44) the error was great if the proportion of carotenoids to vitamin A was large.

The vitamin A in cod liver oil was susceptible to heat and to oxidation, being destroyed by aeration at 98° C. for 75 min. (Wokes and Willimott (46)). Similar results were reported by Sherman *et al.* (40) and Robinson (39). It was not immediately clear whether vitamin A *per se* was unstable, or whether it was attacked only by other constituents of the oil of which it formed a part.

The presence of such constituents of the oil itself might cause oxidation, as suggested by Dann (6), especially unsaturated acids such as oleic acid (Emmerie (13), Smith and Hazley (41), Norris and Church (36)).

These suspicions were confirmed when Heilbron *et al.* (19) isolated vitamin A as a yellow viscous oil and found that it was unexpectedly resistant to oxidation, decreasing in potency by only 10% in one month. Similar observations were reported by Edisbury *et al.* (10). It then appeared essential to separate the non-saponifiable matter containing the sterols and vitamin A from the remainder of the oil, especially the unsaturated fatty acids.

Accordingly, the presence of inhibiting substances in the saponifiable fraction has led to the acceptance of saponification as a preliminary step in the determination of vitamin A in relatively poor sources of the vitamin, such as liver, milk, and even the poorer grades of fish-liver oils. The extra handling entailed by this procedure has necessitated detailed research concerning the behaviour of the vitamin.

It is realized that major discrepancies may arise with diluted oils as received in the laboratory, according to the nature and condition of the diluting oil. Dyer *et al.* (9) stated that equal quantities of vitamin A dissolved in arachis, coconut, and cottonseed oils, and in ethyl laurate, showed great variability

in their biological activity. The significance of this is not entirely clear, yet it is certain that unsaturation in the diluting oil is deleterious to vitamin A. Hence, hydrogenated cottonseed oil is recommended as a diluent in standard reference oils (Neal *et al.* (35)).

The final correlation of the chemical and the biological method must await:

(1) Further knowledge about the biological effect of the diluting medium,

(2) The availability of synthetic vitamin A.

Bearing this in mind, the writer outlines, in this paper, the actual technique of the chemical method with particular regard to reproducibility of results. The conversion factor chosen must necessarily be regarded as somewhat arbitrary. Accordingly, stress is not laid on the absolute figures, but on details of procedure that are designed to amplify the rather inadequate instructions so far published.

Storage of Material

Because it is not always possible to proceed with saponification until after a period of storage, the question arises as to how rapidly vitamin A is lost. According to most authors, samples of oil should be used fresh, and the air above the oil replaced by nitrogen or carbon dioxide.

Jensen and With (21) reported that liver specimens could be stored with safety in a refrigerator for at least 72 hr., and that even 10 days' storage was accompanied by a loss of less than 10%. Moore (30), after examining more that 1000 samples of human livers, stated that there was no deterioration of vitamin A during storage, sampling, and processing.

Saponification

The usually accepted procedure is to saponify with potassium hydroxide in ethyl alcohol, although Holmes and Corbet (20) used isopropyl alcohol. The saponification mixtures used by various workers are listed in Table I, but reasons for using the particular quantities stated were not usually given.

The time of saponification suggested in the literature ranges from two minutes to one hour, according to nature and size of sample. It seems that since vitamin A is remarkably stable in hot alkaline solution (Dann (6)), saponification for a longer time than strictly necessary has no harmful effect.

Extraction of Non-saponifiable Matter from Alcoholic Soap Solution

The reagents used by other workers were:

(1) Ethyl ether—Wilson (45), Dann and Evelyn (7), Morton and Creed (33), French (16), Moore (31), Koehn (23), Molteno and Rapson (29), Heilbron *et al.* (18), and others.

(2) Petroleum ether (light petroleum)—Norris and Church (36), Karrer *et al.* (22), Holmes and Corbet (20), LePage and Pett (24), Molteno and Rapson (29), McFarlane and Sutherland (27).

(3) Chloroform—Coward *et al.* (4), Smith and Hazley (41).

TABLE I

COMPOSITION OF SAPONIFICATION MIXTURES USED BY DIFFERENT AUTHORS

Authors	Saponification mixture
Edisbury *et al.* (11)	0.5 ml. of 60% aqueous potash 10 ml. of 95% ethyl alcohol per gm. of oil
Dann and Evelyn (7)	2 ml. of 60% aqueous potash 10 ml. of 95% ethyl alcohol per gm. of oil
French (16)	10 ml. of 77% alcohol saturated with potash per gm. of oil
Norris and Church (36)	2 ml. of 20% alcoholic potash per gm. of oil
Jensen and With (21)	4 ml. of 5% alcoholic potash per gm. of liver
Andersen and Nightingale (1)	0.4 ml. of 56% aqueous potash 10 ml. of 95% ethyl alcohol per gm. of butter
Morgareidge (32)	3 ml. of 50% aqueous potash 35 ml. of 95% ethyl alcohol per gm. of oil

(4) Methylated ether—Andersen and Nightingale (1).

(5) Methylene chloride—Tompkins and Bolomey (43).

Objections have been raised that vitamin A is unstable in chloroform, although this is denied by Embree (12). Thorbjarnarson and Drummond (42) used chloroform in their preliminary extraction process prior to vitamin A estimation.

Methylene chloride has lately been advocated for whole oils, but cannot be used for unsaponifiable matter owing to permanent emulsification (43).

Most workers record the use of either ethyl ether or petroleum ether (light petroleum) for the extraction process. The latter has been advocated on grounds of economy and also because it was maintained that its use resulted in better separation of the two layers, with less tendency to emulsification.

According to Smith and Hazley (41): "light petroleum is notoriously inefficient for extraction of non-saponifiable matter, seven portions totalling 600 ml. giving only 94 per cent extraction of the vitamin from 5 g. of cod liver oil." Gillam and Senior (17) stated that vitamin A distributed itself equally between 90% methyl alcohol and light petroleum, whereas with 70% methyl alcohol, partition was eight to one in favour of light petroleum, necessitating at least seven extractions. They were unable to obtain quantitative extraction with petroleum ether, whereas Smith and Hazley obtained 100% extraction with ethyl ether, using three changes of the solvent instead of seven.

The significance of the composition of the original saponification mixtures and the dilution of the mixtures with water before extraction seemed to merit investigation. Some authors mentioned dilution of the alcoholic soap solution with one (21, 24), two (36), three (23, 34), or four (20, 35) volumes of water. In many cases it was not even mentioned as a necessary step.

Yudkin (48) presented figures for the vitamin A content of blood serum, demonstrating clearly the difference between the results obtained with ethyl ether and with petroleum ether. His figures showed that saponification followed by light petroleum extraction gave consistently lower results than when ethyl ether was used. On the other hand, the same worker found that simple extraction without saponification gave equally good results with both solvents. This is direct evidence that it is a question of partition rather than of solubility.

Washing

The procedure of washing usually recommended is as follows:

100 ml. water	No shaking
10 ml. water	Shaking
100 ml. water	No shaking
10 ml. $N/6$ potassium hydroxide	Shaking

followed by as many changes of water as are necessary in order that the final rinse may show no cloudiness with 10% hydrochloric acid.

It seemed that it would be advantageous to study the washing procedure more thoroughly in order to establish a technique involving the minimum loss of ether.

Drying

Dann and Evelyn (7) and Norris and Church (36) originally stated that traces of moisture did not affect the development of the blue colour; most other workers, however, stressed the importance of complete drying (1, 23, 47). It is now generally realized that, whereas the blue colour does develop in the presence of moisture, the cloudiness accompanying such a solution causes high readings on the colorimeter. The drying procedure was therefore investigated, chiefly in regard to economy of solvent.

Antimony Trichloride Solution

Variable percentages of antimony trichloride by weight were given in the literature:

Dann and Evelyn (7)	20%
Pharmacopoeia Commission (38)	21 to 23%
Koehn and Sherman (23)	22.5%
Wokes and Willimott (47)	22 to 24%
Brode and Magill (3)	Saturated

Specially purified chloroform dissolved less antimony trichloride than ordinary chloroform (Heilbron *et al.* (18)); it is known that the formation of a saturated solution is dependent mainly on the purity of the chloroform used, since even 1% of alcohol raises the solubility of antimony trichloride in chloroform to 38% (38).

A thorough investigation of the various steps in the determination of vitamin A was carried out, particular regard being paid to the extraction, washing, and drying procedures.

Experimental

Storage of Material

Other workers have stated, and it is here confirmed, that no loss of vitamin A occurred when samples were kept in an alcoholic alkaline solution overnight, or even for 24 hr. Nevertheless a practice was made of processing the sample immediately after collection; for deterioration within the sample itself, due to the influence of fat autoxidation (Dann (6)), is a factor that is difficult to control, so that fresh material is desirable.

Saponification Mixture

It is evident from Table I that different amounts of potassium hydroxide have been used. In this work a detailed examination in regard to the most suitable amount was carried out. The results show that any excess of potassium hydroxide, over and above that indicated by the saponification number of the fat, did not affect the vitamin A itself. The use of a large excess of potash, however, introduced two difficulties that caused trouble at a later stage:

(1) Emulsification at the interface made accurate separation of the two layers impossible,

(2) It entailed extra washing.

Both of these difficulties caused mechanical loss of ether at the separatory funnel stage. Accordingly, the accurate amount of potash necessary to give the small excess for complete saponification is recommended, and this amount should in no circumstances be exceeded. The time of saponification was varied between 30 min. and three hours, with no effect on the results. The procedure adopted therefore was to regard saponification as complete immediately the solution became homogenous. The time varied with the nature, amount, condition, and state of subdivision of the sample. Five minutes was ample for a 500 mg. sample of a fish liver oil, and for a 20 ml. sample of milk or colostrum. A five gram sample of liver took between 30 and 45 min.

Solvent

The type and amount of solvent to be used in vitamin A determinations has an important economic significance to workers doing a large number of determinations. Since the two most widely used solvents are ethyl ether and petroleum ether (light petroleum), a study was made of the relative efficiency of these two, from both the quantitative and manipulative aspects. The work of Smith and Hazley (41), Gillam and Senior (17) and Yudkin (48) throws doubt on the suitability of petroleum ether in the partition technique, although vitamin A is itself soluble in this solvent.

Repeated determinations were carried out on one diluted fish liver oil, identical techniques, except for the different solvents, being used. It was found that results obtained with petroleum ether were entirely unpredictable, whereas ethyl ether always extracted like amounts of vitamin A (Table II). Nor did dilution of the soap solutions with different amounts of water, prior to extraction, give a more consistent partition with petroleum ether (Table III).

TABLE II

VITAMIN A VALUES OBTAINED WITH TWO DIFFERENT SOLVENTS IN REPEATED DETERMINATIONS ON ONE SAMPLE OF FISH LIVER OIL

International units per gram

Extracted with petroleum ether	Extracted with ethyl ether
789, 473, 360, 765, 522, 348, 613, 717, 818, 482, 625, 664, 664, 664, 418, 327.	1155, 1165, 1180, 1198, 1260, 1250.

TABLE III

EFFECT OF DILUTION OF THE ORIGINAL SOAP SOLUTION, PRIOR TO EXTRACTION WITH PETROLEUM ETHER OR ETHYL ETHER, ON VITAMIN A VALUES OF THE SAME FISH LIVER OIL

Dilution with:	International units of vitamin A	
	Petroleum ether	Ethyl ether
2 volumes of water (to 26% alcohol)	472	1178
3 volumes of water (to 19% alcohol)	763	1200
4 volumes of water (to 16% alcohol)	348	1153

Even if, as Gillam and Senior stated (17), 89% extraction could be obtained with petroleum ether, it needed as least seven extractions. Consequently the economic advantage of this cheaper solvent disappeared. The use of large quantities of solvent and the necessity for large apparatus was avoided by using ethyl ether, with which solvent three extractions were always sufficient.

It has been stated that petroleum ether is preferable to ethyl ether in so far as emulsification is less likely to occur (27). According to our technique, emulsification with ethyl ether was avoided altogether, provided that:

(1) The soap solution was correctly diluted with water before extraction,

(2) A large excess of potash was avoided in saponification.

Under these circumstances there was no need to add absolute ethyl alcohol to help separation into two layers, as recommended by some workers. Separation took place rapidly, even after the most vigorous and prolonged shaking, resulting in a fine, clearcut line between the two phases in three minutes. Any difficulty at this stage was due to failure to adjust the previous procedure and had to be corrected. For emulsification at the interface from whatever cause led to loss of some of the ethereal phase when the lower layer was drawn off.

Washing

In any two phase system of partially miscible liquids, such as ether and water, each phase has a constant composition, irrespective of the amounts of the two components present. At equilibrium the aqueous layer is saturated

with ether and the ether layer with water. So it must be realized that the water layer in the repeated washings that are withdrawn and discarded is saturated with ether at that temperature. Excessive washing with large quantities of water was therefore avoided, to minimize loss of ether. That such loss is considerable could be seen by measuring the volume of the remaining ether solution before and after washing. For this reason it was decided to omit entirely the second washing with 100 ml. of water.

Separation during washing was as complete as in the extraction process. The only slight emulsification occasionally to occur was after shaking with 10 ml. of $N/6$ potash, and then only when the free fatty acid content was high. It was found to be very important that none of the emulsion (which existed *below* the dividing line) was discarded with the washings. It cannot be too strongly emphasized that low results are often attributable to incorrect procedure in the phase separation.

Drying

After the last washings had been removed, the inside of the separatory funnel below the tap was dried carefully with a spill of filter paper. Usual instructions recommend that the ethereal solution at this point be run through one inch of loosely packed anhydrous sodium sulphate on a sintered glass plate. It was found that this was unsatisfactory. Thirty to forty millilitres of ethereal solution did not run through the layer of sodium sulphate but was to some extent held there. The use of pressure from above, or suction from below, served to pull most of it through, but there always remained some adhering to the sodium sulphate. This could be washed through with fresh ether, but two changes were necessary. This increased the volume of ethereal solution to be evaporated down, entailing a large loss of this solvent. In repeated experiments as much as 25% of the vitamin A was held back in this way in the filtration process.

It was found much more economical and accurate to dry the ether solution, kept to as small a volume as possible, *over* anhydrous sodium sulphate; this was then decanted into a volumetric flask and adjusted to the desired volume; a further quantity of anhydrous sodium sulphate was added to ensure a dry aliquot. One millilitre of such a solution always gave perfectly clear solutions when treated with chloroform and antimony trichloride reagent.

Light

The complete procedures were done respectively in bright indoor light, and in a dark room using subdued green light only. We were unable to substantiate Embree's statement (12) that ultra-violet light caused breakdown of the vitamin when in dilute ether solution. Nor did we find it necessary to follow the advice of Andersen and Nightingale (1), who suggested collecting the extracted material in porcelain beakers, to avoid transmitted light as much as possible.

Antimony Trichloride Reagent

Many grades of commercial chloroform contain quite significant quantities of alcohol; a practice was therefore made of using only a solution that was saturated at room temperature with respect to the particular chloroform used. Such a solution, stored in the dark at room temperature, could be used over a period of days or even weeks. Owing to the difference in solubility of antimony trichloride in chloroform at the two temperatures, the reagent should not be kept in the refrigerator and then used at room temperature.

Development of the Blue Colour

One millilitre of ethereal solution was pipetted into an Evelyn colorimeter tube and evaporated to dryness below 40° C. with the help of light suction. The residue was taken up in 1 ml. of *dry* chloroform and the tube placed in the colorimeter with filter No. 620 in place. Nine millilitres of the antimony trichloride reagent was run rapidly into the tube, held two inches up in the socket. Mixing was almost instantaneous, and when the tube was at once lowered into position, the reading was taken. If the antimony trichloride reagent was saturated, the blue colour persisted long enough to ensure easy reading. Aliquots could be made to correspond to the nearest unit on the scale. A blank consisting of 1 ml. of dry chloroform and 9 ml. of the antimony trichloride reagent was set at 100.

When the precautions here outlined were followed, one worker was able to run two parallel samples, from the original weighing of material to the reading of the colorimeter, in one and one-half to two hours, according to manipulative ability. Any emulsification at the interface increased this time to as much as four hours, but this disadvantage was avoided by rigid compliance with the above instructions and the practice afforded by repetition.

Discussion

The steps in the conversion of the galvanometer reading G to international units were given by Dann and Evelyn (7). The conversion factor by which the E value is multiplied to give international units has varied continually ever since the extinction coefficient was worked out. Early workers used the factor 1600, and as time passed this was increased to 2100 and even to 2290 (20, 23, 28, 32, 35).

Coy *et al.* (5) have done extensive work on conversion factors, with the following results: 2370 was the average factor for a number of whole cod liver oils, whereas 2700 was the factor for the unsaponifiable matter of these same oils. The only explanation given by these workers for the two values is that there are present in low potency oils, and especially in their non-saponifiable matter, substances that have biological activity similar to vitamin A but do not have maximum absorption at 328 $\mu\mu$. Since all the chemical tests in this work were done on the unsaponifiable matter only, the factor 2700 was employed throughout.

The calculation then became:

$$\frac{(2-\log G) \times 0.5 \times 52.5 \times 2700}{\text{milligrams of sample in aliquot}} = \begin{array}{c}\text{International Units of vitamin A} \\ \text{per gram.}\end{array}$$

It is suggested that the final word on the conversion factor must await:

(i) The synthesis of vitamin A,

(ii) Further study on the biological assay of vitamin A, having special regard to the balance between it and other vitamins, .uch as vitamin E.

Until these advances have been made, it is idle to compare the two methods quantitatively. Although the exact correlation between the two methods cannot be stated in absolute values at this time, the chemical method as outlined above is suitable for all comparative work. It is reproducible on aliquots of the same sample and on different samples of the same material.

Attention is drawn, however, to the necessity of careful precautions in extraction, washing, and drying, because it is possible to sustain losses of vitamin A up to 25% during these procedures. According to our findings, faulty technique is more likely to cause low results than decomposition of the vitamin during sampling, saponification, or development of the blue colour.

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CONTRIBUTION TO THE STUDY OF 1,1-DIPHENYLINDAN AND ITS DERIVATIVES. SYNTHESIS OF 1,1-DIPHENYL-3-INDANACETIC AND 1,1-DIPHENYL-3-INDENEACETIC ACIDS[1]

By Paul E. Gagnon[2], L. Gravel[2], and Louis-Philippe Amiot[3]

Abstract

1,1-Diphenylindan was treated with one molecule of bromine. It yielded a monobromide, which was condensed with methyl and ethyl alcohols, piperidine, *p*-toluidine, and aniline. With aqueous solutions of potassium carbonate, the monobromide directly gave rise to 1,1-diphenylindene and small quantities of diphenylindanyl ether.

The condensation of the monobromide with sodium ethyl malonate yielded ethyl 1,1-diphenyl-3-indanmalonate from which 1,1-diphenyl-3-indanmalonic and 1-1-diphenyl-3-indanacetic acids were prepared. A few derivatives of these acids were also obtained.

To establish the constitution of 1,1-diphenyl-3-indanacetic acid and, hence, that of the monobromide and of the other compounds, this acid was prepared directly from 3,3-diphenyl-1-indanone by a Reformatsky reaction with ethyl bromoacetate.

The method of preparation of 1,1-diphenylindan has been improved, 1,1-diphenylindene has been obtained by new methods, and the following compounds are described, as far as the authors are aware, for the first time: 3-bromo-1,1-diphenylindan, 3-methoxy-1,1-diphenylindan, 3-ethoxy-1,1-diphenylindan, 3-N-piperidyl-1,1-diphenylindan, N-phenyl-1,1-diphenyl-3-indanamine, N-*p*-tolyl-1,1-diphenyl-3-indanamine, ethyl 1,1-diphenyl-3-indanmalonate, 1,1-diphenyl-3-indanmalonic acid, 1,1-diphenyl-3-indanmalonic acid *p*-nitrobenzyl ester, silver salt of 1,1-diphenyl-3-indanmalonic acid, 1,1-diphenyl-3-indanacetic acid, 1,1-diphenyl-3-indanacetic acid *p*-nitrobenzyl ester, silver salt of 1,1-diphenyl-3-indanacetic acid, 1,1-diphenyl-3-indanacetanilide, 1,1-diphenyl-3-indanacetamide, 1,1-diphenyl-3-indanacetonitrile, 1,1-diphenyl-3-indanethylamine hydrochloride, ethyl 3-hydroxy-1,1-diphenyl-3-indanacetate, ethyl 1,1-diphenyl-3-indeneacetate, 1,1-diphenyl-3-indeneacetic acid, silver salt of 1,1-diphenyl-3-indeneacetic acid, 1,1-diphenyl-3-indeneacetic acid *p*-nitrobenzyl ester, ethyl 1,1-diphenyl-3-indanacetate.

Introduction

For many years it was known that a few natural products had the property of regulating the growth of plants, but it was not known to which agent the activity of these products was due.

In 1934, Kögl, Haagen-Smit, and Erxleben (12), isolated indolylacetic acid from human urine and a few yeasts and showed that it was this acid that made the above products active.

After this discovery, many workers studied the plant-growth regulating activities of compounds having a constitution approaching that of indolylacetic acid.

Among the numerous compounds studied, 3-indeneacetic acid was found to affect the growth of *Avena* and *Pisum* (19). It was thought that acid

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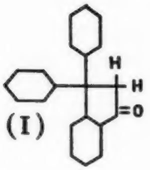
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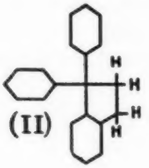
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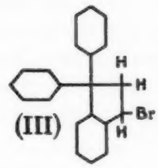
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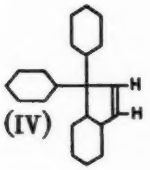
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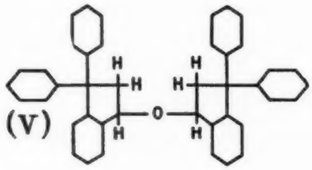
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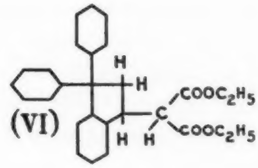
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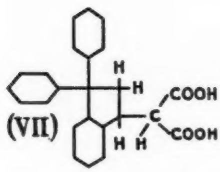
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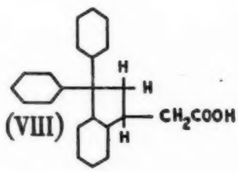
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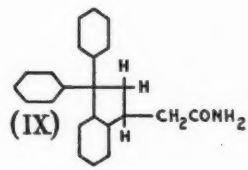
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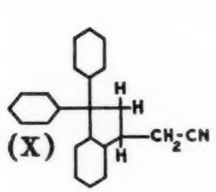
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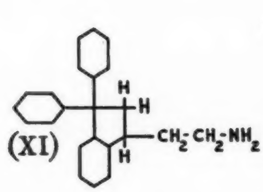
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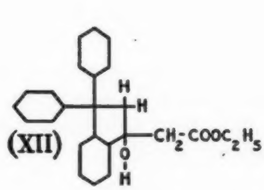
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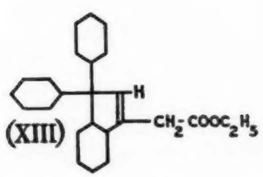
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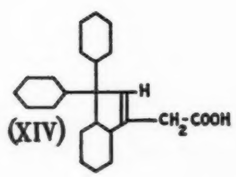
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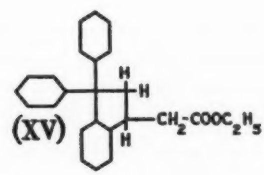
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derivatives of 1,1-diphenylindene and 1,1-diphenylindan would have similar properties, and the object of the present work was the preparation of such acids as well as the study of 1,1-diphenylindan and its derivatives.

As starting material, diphenylindanone (I) (9, 14) was used. This ketone was first reduced to 1,1-diphenylindan (II). The method of preparation has already been described (9, 10); the present authors have studied it in detail.

They found that there was a great advantage in modifying it so as to purify the hydrocarbon obtained, not by treatment with animal black and crystallization in methyl alcohol, but rather by distillation under reduced pressure and subsequent crystallization.

1,1-Diphenylindan was then treated with bromine. Equivalent quantities of hydrocarbon and bromine were used and a 1,1-diphenylindan monobromo derivative (III) was formed. The bromine atom in this compound is in Position 3 with regard to the two phenyl groups, as will be shown later; only one compound was obtained and the reaction seemed to be quantitative.

One of the hydrogen atoms in Position 3 is therefore more easily replaced by bromine than the hydrogen atoms in Position 2; this is undoubtedly due to the presence of the phenyl groups in Position 1.

The bromine atom in the molecule of 3-bromo-1,1-diphenylindan can easily be replaced by another group. When this substance is heated with methyl or ethyl alcohol, the corresponding methoxy and ethoxy derivatives were formed.

With piperidine, aniline, and *p*-toluidine, substituted amines were obtained. For example, with one molecule of monobromide and two molecules of aniline, one molecule of N-phenyl-1,1-diphenyl-3-indanamine, in addition to one molecule of aniline hydrobromide, was formed.

In order to find a more practical method for preparing 1,1-diphenylindene, the authors tried to make, from diphenylindan monobromide, the corresponding hydroxy derivative. By dehydration of this derivative, they hoped to obtain 1,1-diphenylindene.

They treated the monobromide with an aqueous solution of potassium carbonate. However, the product obtained was not 3-hydroxy-1,1-diphenylindan, but 1,1-diphenylindene (IV) (9) and a small quantity of 1,1-diphenyl-3-indanyl ether (V).

Similar results were obtained when 1,1-diphenylindan monobromide was treated with an aqueous solution of potassium hydroxide. Under the experimental conditions, 3-hydroxy-1,1-diphenylindan, formed as an intermediate product, is doubtless unstable, since it could not be isolated. It immediately loses one molecule of water to give rise to 1,1-diphenylindene, or one molecule of water is eliminated from two molecules of hydroxy derivative to form 1,1-diphenyl-3-indanyl ether.

3-Bromo-1,1-diphenylindan was found to have properties similar to those of the halogen derivatives of indan.

1-Bromoindan and 1-chloroindan easily react with aromatic amines to give secondary amines (6, 7, 8).

In the presence of sodium, 1-chloroindan gives with methyl or ethyl alcohol the corresponding methoxy or ethoxy derivatives (22).

The method used to obtain the hydroxyindan consists merely in treating 1-chlorindan with an aqueous solution of potassium carbonate (22); this was

the method applied to 3-bromo-1,1-diphenylindan. The instability of 3-hydroxy-1,1-diphenylindan can then be attributed to the presence in the molecule of two phenyl groups in Position 1 since, even if the method of preparation be changed, for example, if 3-methoxy-1,1-diphenylindan be treated with 48% hydrobromic acid, the product formed is 1,1-diphenylindene and not the hydroxy derivative.

Acids containing the diphenylindan ring were obtained when 3-bromo-1,1-diphenylindan was treated with monosodium ethyl malonate.

The ethyl 1,1-diphenyl-3-indanmalonate (VI) obtained was purified by distillation under reduced pressure and saponified by means of an aqueous solution of potassium hydroxide. The potassium salt was decomposed with dilute sulphuric acid; this yielded 1,1-diphenyl-3-indanmalonic acid (VII). The molecular weight of this acid was determined by analysis of its silver salt. Another derivative, the *p*-nitrobenzyl ester, was prepared by Reid's method (18).

When heated, 1,1-diphenyl-3-indanmalonic acid was transformed into 1,1-diphenyl-3-indanacetic acid (VIII).

The molecular weight of the latter acid was also determined by analysis of its silver salt; in addition, the following derivatives were prepared: *p*-nitrobenzyl ester, anilide, amide, and, from the amide, the corresponding nitrile and amine.

The *p*-nitrobenzyl ester of 1,1-diphenyl-3-indanacetic acid was also prepared by Reid's method. To obtain the anilide and the amide, the authors tried to prepare a chloride by treating 1,1-diphenyl-3-indanacetic acid with thionyl chloride (11). They were unable to isolate the chloride, however, as it is very soluble in most solvents and is easily decomposed.

The reaction of aniline and ammonia on this chloride gave rise to 1,1-diphenyl-3-indanacetanilide and 1,1-diphenyl-3-indanacetamide (IX) respectively.

1,1-Diphenyl-3-indanacetamide gave with hydrochloric acid a compound containing one molecule of hydrochloric acid for each molecule of amide. When treated with a dehydrating agent, it lost one molecule of water to yield 1,1-diphenyl-3-indanacetonitrile (X) (11).

By the reduction of the nitrile with sodium and alcohol, 1,1-diphenyl-3-indanethylamine (XI) was prepared, but it was isolated as hydrochloride.

None of the results obtained so far could show precisely the position of the bromine atom in the diphenylindan monobromide molecule.

The constitution of all the compounds obtained was definitely established by preparing for the first time 1,1-diphenyl-3-indanacetic acid (VIII) by another method that leaves no doubt as to its constitution, and by identifying this acid with the monobasic acid previously obtained from diphenylindan monobromide.

For this purpose, a Reformatsky reaction was carried out (1, 15, 16) with diphenylindanone, by treating ethyl bromoacetate and granulated zinc with the ketone dissolved in a mixture of benzene and toluene. As is well known,

this general reaction proceeds in three stages (17). In the present case, the product obtained was ethyl 3-hydroxy-1,1-diphenyl-3-indanacetate (XII).

When a current of hydrogen chloride gas was passed through a solution of the compound in anhydrous toluene, dehydration took place and an unsaturated ester was isolated. The method is analogous to that used by Natelson and Gottfield (15).

Dehydration of β-hydroxy esters brings about the formation of a double bond between the α- and β- or the β- and γ-carbon atoms, and the amounts of each of the products formed depend on the dehydrating agents used and on the conditions of the reaction (13).

However, the authors believe that the unsaturated ester obtained in this case is ethyl 1,1-diphenyl-3-indeneacetate (XIII).

Since 3-hydroxy-1,1-diphenylindan is unstable, immediately giving rise to 1,1-diphenylindene by the loss of one molecule of water, as was previously shown, the double bond is probably formed inside the ring between the β- and γ-carbon atoms when ethyl 3-hydroxy-1,1-diphenyl-3-indanacetate is dehydrated. If the double bond had been formed outside the ring, between the α- and β-carbon atoms, *cis*- and *trans*-isomers would have been possible, but the authors could isolate only one compound.

It is true that the distillation of ethyl 1-hydroxy-1-indanacetate caused the dehydration of this substance with the formation of a double bond outside the ring (1), but 1-hydroxyindan is much more difficult to dehydrate to indene than 3-hydroxy-1,1-diphenylindan to the corresponding hydrocarbon.

Moreover, many examples are given in the literature, where, by dehydration of cyclic β-hydroxy esters, a double bond inside the ring is formed, for example, the dehydration of ethyl 1-hydroxy-cyclohexylacetate, which yields ethyl 1-cyclohexenylacetate (21), and that of ethyl 1-hydroxy-α,α,2-trimethylcyclopentylacetate, which gives rise to ethyl α,α,2-trimethylcyclopentenylacetate.

If we accept it as true that the unsaturated ester obtained is ethyl 1,1-diphenyl-3-indeneacetate, the acid that was obtained from it by saponification was 1,1-diphenyl-3-indeneacetic acid (XIV).

Two derivatives of this acid were prepared, the silver salt and the *p*-nitrobenzyl ester.

To obtain 1,1-diphenyl-3-indanacetic acid (VIII), which was particularly interesting in this case, two methods were used: *(a)* hydrogenation of the unsaturated ester (XIII) and subsequent saponification of the product obtained, and *(b)* hydrogenation of 1,1-diphenyl-3-indeneacetic acid (XIV).

The authors are certain that 1,1-diphenyl-3-indanacetic acid, prepared from diphenylindanone by the Reformatsky reaction, was identical with the monobasic acid prepared from diphenylindan monobromide. A mixed melting point determination verified the identity of these substances, and the derivatives obtained from the acid prepared by the two different methods were

shown to be identical. The derivatives were the anilide, the amide, and the *p*-nitrobenzyl ester.

The constitution of the substances prepared by the authors is therefore well established.

Experimental Part

1,1-Diphenylindan (II)

Clemmensen's method (3, 4, 5) modified by Gagnon and Charette (10) was used to reduce diphenylindanone (I). The hydrocarbon obtained was purified, not by treatment with animal black and crystallization in methyl alcohol, but by distillation under reduced pressure and subsequent crystallization. It was identified as 1,1-diphenylindan by means of a mixed melting point determination: m.p. 67° C.*

3-Bromo-1,1-diphenylindan (III)

In a round bottomed flask (200 ml.), 1,1-diphenylindan (21.57 gm.) was dissolved in anhydrous carbon disulphide (75 ml.). The flask was fitted with a reflux condenser and the solution brought to the boiling point. A solution of bromine (12.72 gm.) in anhydrous carbon disulphide (25 ml.) was added, drop by drop, and the mixture was kept boiling until hydrogen bromide was completely eliminated. After cooling, the reaction mixture was poured into a separatory funnel, washed with an aqueous solution of sodium bicarbonate and with water and finally dried over anhydrous sodium sulphate. After filtration, the solvent was distilled off and the residue crystallized twice from acetic acid. Finally, the crystals were washed with methyl alcohol: m.p. 87 to 88° C. Yield, 23.1 gm. (86%). 3-Bromo-1,1-diphenylindan is very soluble in benzene, toluene, petroleum ether, carbon disulphide, ether, and chloroform. Calc. for $C_{21}H_{17}Br$: Br, 22.89%. Found: Br, 22.70%.

3-Methoxy-1,1-diphenylindan

3-Bromo-1,1-diphenylindan was treated with methyl alcohol and the mixture was boiled until the evolution of hydrogen bromide ceased. After cooling, a colourless product crystallized out; m.p. 101 to 102° C. Calc. for $C_{22}H_{20}O$: C, 88.00%; H, 6.67%. Found: C, 86.88%; H, 6.53%.

3-Ethoxy-1,1-diphenylindan

A mixture of 3-bromo-1,1-diphenylindan and ethyl alcohol was boiled until the evolution of hydrogen bromide ceased. After cooling, a colourless product crystallized out: m.p. 70 to 71° C. Calc. for $C_{23}H_{22}O$: C, 87.89%; H, 7.0%. Found: C, 87.21%; H, 7.11%.

3-[Piperidyl]-1,1-diphenylindan

3-Bromo-1,1-diphenylindan (2.5 gm.) and piperidine (1 ml.) were dissolved in dry benzene (25 ml.) and the mixture was heated on a water-bath for half an hour. Piperidine hydrobromide precipitated and was filtered off. Concentrated hydrochloric acid was then added to the filtrate and the mixture vigorously stirred. A voluminous precipitate was formed. Water was added to

* *Melting points are uncorrected.*

dissolve the piperidine hydrochloride and the residue was filtered off, washed with water and with alcohol, and dried; m.p. 253 to 255° C. Calc. for $C_{26}H_{28}NCl$: Cl, 9.12%. Found: Cl, 9.52%. In order to obtain the free amine, the hydrochloride was dissolved in ethyl alcohol and an alcoholic solution of potassium hydroxide was added until the solution was alkaline to litmus. The amine precipitated and was recrystallized from methyl alcohol: m.p. 108 to 109° C. Calc. for $C_{26}H_{27}N$: C, 88.38%; H, 7.65%. Found: C, 87.06%; H, 8.0%.

N-Phenyl-1,1-diphenyl-3-indanamine

In a flask (50 ml.), 3-bromo-1,1-diphenylindan (4 gm.) was dissolved in aniline (3 gm.) and the solution was heated on a water-bath for 15 min. A precipitate of aniline hydrobromide soon formed. The solution was then diluted with benzene and filtered. In order to distil off the benzene and the excess of aniline a current of steam was passed through the filtrate until the distillate was limpid. On cooling, a resinous mass, which rapidly solidified, was formed in the distilling flask at the surface of the water. This mass was soluble in benzene but less soluble in petroleum ether, from which a crystalline product was obtained. This product was recrystallized twice in glacial acetic acid; m.p. 125 to 126° C. Yield, 3.2 gm. (77%). Calc. for $C_{27}H_{23}N$: C, 89.75%; H, 6.35%. Found: C, 88.92%; H, 6.7%. To obtain the hydrochloride, the amine was dissolved in the smallest possible quantity of anhydrous ether and a current of dry hydrogen chloride was passed through the solution. The hydrochloride immediately separated in white crystals; it was then filtered off and washed with ether; m.p. 213 to 214° C. Calc. for $C_{27}H_{24}NCl$: Cl, 8.93%. Found: Cl, 8.89%.

N-p-Tolyl-1,1-diphenyl-3-indanamine

3-Bromo-1,1-diphenylindan (3 gm.) was mixed in a mortar with *p*-toluidine (2 gm.). The mass soon became viscous and finally a liquid containing crystals in suspension was formed. This mixture was poured into a flask and heated for one hour on a water-bath. After cooling, benzene (25 ml.) was added and *p*-toluidine hydrobromide was filtered off. The filtrate was washed with dilute hydrochloric acid and with water. The benzene was distilled off, the residue was dissolved in anhydrous ether, and a current of dry hydrogen chloride was passed through the solution. The amine hydrochloride precipitated immediately. It was filtered off and washed many times with water and with ether; m.p. 218 to 219° C. Yield, 3 gm. (86%). Calc. for $C_{28}H_{26}NCl$: Cl, 8.64%. Found: Cl, 8.53%. To obtain the free amine, the hydrochloride was dissolved in the smallest possible quantity of alcohol and an alcoholic solution of sodium hydroxide (10%) was added until the solution was alkaline to litmus. The amine separated as a viscous mass when water was added, but it soon solidified. It was filtered off, washed with alcohol and crystallized from petroleum ether; m.p. 124 to 125° C. Calc. for $C_{28}H_{25}N$: C, 89.6%; H, 6.66%. Found: C, 89.07%; H, 6.3%.

1,1-Diphenyl-3-indanyl Ether (V)

In a flask (100 ml.) fitted with a reflux condenser, 3-bromo-1,1-diphenylindan (5 gm.) was treated for four hours with a boiling aqueous solution of potassium carbonate (4%) (50 ml.). The aqueous portion was then separated by decantation. The residue was treated with boiling petroleum ether, in which it partly dissolved. The insoluble part was separated by filtration and crystallized in benzene and acetic acid. The 1,1-diphenyl-3-indanyl ether thus obtained was quite white; m.p. 192 to 195° C. Calc. for $C_{42}H_{34}O$: C, 90.97%; H, 6.32%. Found: C, 89.4%; H, 6.33%. The portion soluble in petroleum ether was washed with water. The solution was dried over anhydrous sodium sulphate and the solvent was distilled off. The residue still contained bromine. It was then treated for two hours with a boiling aqueous solution of potassium hydroxide (4%) (40 ml.). The liquid portion was separated by decantation and the residue was washed with water. This residue was dissolved in methyl alcohol and the solution obtained was treated with bone black and filtered. The solvent was evaporated slowly at room temperature. A white product soon crystallized; m.p. 90 to 91° C. It was identified, by a mixed melting point determination, as 1,1-diphenylindene, already prepared by Gagnon (9).

1,1-Diphenylindene (IV)

In a flask (50 ml.) fitted with a reflux condenser, 3-methoxy-1,1-diphenylindan (1 gm.) was treated for three hours with a boiling solution of hydrobromic acid (48%) (3 ml.). The mixture of water, methyl alcohol, and hydrobromic acid was distilled off under reduced pressure. The residue was dissolved in ethyl alcohol and the solution obtained was treated with bone black and filtered. By evaporation of the solvent, a white product was obtained; m.p. 90 to 91° C. It was identified as 1,1-diphenylindene by a mixed melting point determination. Yield, 0.79 gm. (77%).

Ethyl 1,1-Diphenyl-3-indanmalonate (VI)

In a dried round bottomed flask (500 ml.) containing anhydrous toluene (100 ml.) and powdered sodium, ethyl malonate (15 mg.) was added. The flask was fitted with a reflux condenser connected with a calcium chloride tube and the mixture was kept boiling for two hours. All the sodium having then reacted, a solution of 3-bromo-1,1-diphenylindan (32.5 gm.) in anhydrous toluene (100 ml.) was added and the mixture was kept boiling for three hours. The toluene was distilled off and the residue, a viscous product, which could not be crystallized, was distilled at 268° C. under reduced pressure (1 mm.). Calc. for $C_{28}H_{28}O_4$: C, 78.53%; H, 6.54%. Found: C, 78.54%; H, 6.75%.

1,1-Diphenyl-3-indanmalonic Acid (VII)

Ethyl 1,1-diphenyl-3-indanmalonate was treated with a hot solution of potassium hydroxide (40 gm. in 45 ml. of water) and the mixture was kept boiling for half an hour. After cooling, the potassium salt of 1,1-diphenyl-3-indanmalonic acid crystallized. It was dissolved in a large volume of hot water and the solution obtained was filtered with bone black and cooled to

room temperature. The solution was then slowly poured, with constant stirring, into a beaker containing a dilute solution of sulphuric acid (1000 ml. of water and 50 ml. of concentrated sulphuric acid). A precipitate was formed. After standing for some time, it was filtered off and washed many times with distilled water, and dried in the oven at 80° C. It was crystallized in toluene; m.p. 160° C. 1,1-Diphenyl-3-indanmalonic acid is soluble in methyl alcohol, in ethyl alcohol, and in acetic acid. At 165° C. it decomposed with evolution of carbon dioxide. From 32.5 gm. of monobromide, 28.6 gm. of acid was obtained. Yield, 83%. Calc. for $C_{24}H_{20}O_4 . 2H_2O$: C, 70.6%; H, 5.88%. Found: C, 70.91%; H, 5.88%.

Silver Salt of 1,1-Diphenyl-3-indanmalonic Acid

A paste was prepared by mixing 1,1-diphenyl-3-indanmalonic acid (1 gm.) with a few drops of water. It was dissolved in a few drops of concentrated ammonia, and a slight excess of silver nitrate (0.4 gm.) in dilute solution was added. The silver salt precipitated. The mixture was well stirred, diluted, washed many times with hot water, and dried first in the oven at 80° C. and then in a desiccator containing phosphorus pentoxide. Calc. for $C_{24}H_{18}O_4$ Ag_2 : Ag, 36.86%. Found: Ag, 36.75%.

1,1-Diphenyl-3-indanmalonic Acid p-Nitrobenzyl Ester

1,1-Diphenyl-3-indanmalonic acid (1 gm.) was dissolved in a mixture of water (5 ml.) and alcohol (10 ml.) containing the quantity of sodium hydroxide necessary to neutralize the acid. *p*-Nitrobenzyl bromide was added and the solution was heated to the boiling point. After a few minutes a precipitate was formed and after half an hour the mixture was allowed to cool. The precipitate was filtered off and recrystallized from acetic acid and ethyl alcohol; m.p. 73 to 75° C. Calc. for $C_{38}H_{30}O_8N_2$: C, 71.03%; H, 4.67%. Found: C, 70.78%; H, 5.17%.

1,1-Diphenyl-3-indanacetic Acid (VIII)

1,1-Diphenyl-3-indanmalonic acid was heated in a flask (100 ml.) in an oil-bath at a temperature of 170 to 180° C. until there was no longer any evolution of water vapour and carbon dioxide. The contents of the flask, when cooled, was dissolved in glacial acetic acid. Bone black was added and the solution, having been kept boiling for 15 min., was filtered and allowed to cool. A precipitate was slowly formed. It was filtered off and recrystallized twice from methyl alcohol; m.p. 173 to 174° C. Yield, 15 gm. (85%). 1,1-Diphenyl-3-indanacetic acid is soluble in benzene, toluene, acetic acid, methyl alcohol, ethyl alcohol, carbon tetrachloride, and chloroform; it is insoluble in ethyl ether and petroleum ether. Calc. for $C_{23}H_{20}O_2$: C, 84.02%; H, 6.09%. Found: C, 82.54%; H, 6.44%.

Silver Salt of 1,1-Diphenyl-3-indanacetic Acid

This silver salt was prepared in the same way as the silver salt of 1,1-diphenyl-3-indanmalonic acid. Calc. for $C_{23}H_{19}O_2Ag$: Ag, 24.81%. Found: Ag, 24.45%.

1,1-Diphenyl-3-indanacetic Acid p-Nitrobenzyl Ester

This ester was prepared in the same way as 1,1-diphenyl-3-indanmalonic acid *p*-nitrobenzyl ester. M.p. 172 to 173° C. Calc. for $C_{30}H_{25}O_4N$: C, 77.84%; H, 5.40%. Found: C, 77.48%; H, 5.76%.

1,1-Diphenyl-3-indanacetanilide

A mixture of thionyl chloride (10 ml.) and 1,1-diphenyl-3-indanacetic acid (4 gm.) was placed into a dry flask (50 ml.) fitted with a reflux condenser connected to a calcium chloride tube. The mixture was heated in a water-bath for 25 min. and the excess thionyl chloride was distilled off under reduced pressure. The viscous residue was dissolved in petroleum ether (25 ml.), and aniline (5 ml.) was added, drop by drop, to the solution. A viscous mass that soon solidified was formed. It was filtered off and crystallized in methyl alcohol. The anilide crystallizes in white leaflets; m.p. 171 to 172° C. Calc. for $C_{29}H_{25}ON$: C, 86.35; H, 6.20%. Found: C, 85.82; H, 6.99%.

1,1-Diphenyl-3-indanacetamide (IX)

A mixture of 1,1-diphenyl-3-indanacetic acid (9 gm.) and thionyl chloride (20 ml.) was placed in a flask (50 ml.) fitted with a reflux condenser connected to a calcium chloride tube. The mixture was kept boiling for half an hour. The excess of thionyl chloride was then distilled off under reduced pressure. The viscous residue was dissolved in anhydrous ether (50 ml.) and a current of dry ammonia gas was passed through the solution, which was kept at ice temperature. The amide precipitated. It was filtered off, washed with ether and with water, and dried. Yield, 8.3 gm. (92%). It was recrystallized twice in methyl alcohol; m.p. 181 to 182° C. 1,1-Diphenyl-3-indanacetamide is soluble in methyl and ethyl alcohols and acetic acid; it is slightly soluble in benzene, toluene, petroleum ether, and ethyl ether. Calc. for $C_{23}H_{21}ON$: C, 84.40%; H, 6.42%. Found: C, 83.99%; H, 6.82%.

Action of Hydrochloric Acid on 1,1-Diphenyl-3-indanacetamide

1,1-Diphenyl-3-indanacetamide (2 gm.) was dissolved in a mixture of ether (20 ml.) and alcohol (5 ml.) and a current of hydrogen chloride gas was passed through the solution. A crystalline compound precipitated. It was filtered off, washed with ether, and recrystallized from ethyl alcohol; m.p. 191 to 192° C. A small quantity of this compound was dissolved in the least possible quantity of ethyl alcohol and treated with an aqueous solution of potassium hydroxide. The precipitate formed was filtered off, crystallized from alcohol; it was identified as 1,1-diphenyl-3-indanacetamide by a mixed melting point determination. Calc. for $C_{23}H_{21}ON.HCl$: Cl, 10.04%. Found: Cl, 9.92%.

1,1-Diphenyl-3-indanacetonitrile (X)

A mixture of 1,1-diphenyl-3-indanacetamide (7 gm.) and thionyl chloride (14 ml.) was placed in a flask (50 ml.) fitted with a reflux condenser. The mixture was heated to the boiling point. A thick paste was formed; this liquefied about twenty minutes later. After another 10 min., the excess of thionyl chloride was distilled off under reduced pressure. The residue crystal-

lized and was dissolved in hot petroleum ether. By cooling the solution, two layers were formed and the lower layer soon solidified. The upper liquid layer was separated by decantation and the solid residue after being dissolved in methyl alcohol was treated with bone black. After filtration the alcoholic solution was concentrated by evaporation and a white crystalline product was obtained; m.p. 120 to 121° C. Yield, crude product, 6.5 gm. (98%), purified product, 5.2 gm. (79%). Calc. for $C_{23}H_{19}N$: N, 4.53%. Found: N, 4.55%.

1,1-Diphenyl-3-indanethylamine (XI)

In a flask (250 ml.) fitted with a reflux condenser, 1,1-diphenyl-3-indanacetonitrile (3 gm.) was dissolved in absolute ethyl alcohol (35 ml.). The solution was heated in a water-bath and metallic sodium (6 gm.) was added in small portions. When all the sodium had reacted, water (800 ml.) was added and the amine separated. The amine was extracted with ether, the ethereal solution washed with water and dried over anhydrous sodium sulphate. After filtration, a current of dry hydrogen chloride was passed through the solution. The hydrochloride of the amine precipitated. It was filtered off, washed with ether and dried first in the oven at 80° C. and then in a desiccator containing potassium hydroxide; m.p. 180 to 185° C. Yield: 2.8 gm. (82%). Calc. for $C_{23}H_{24}NCl$: Cl, 10.15%. Found: Cl, 9.76%.

Ethyl 3-Hydroxy-1,1-diphenyl-3-indanacetate (XII)

Into a dry apparatus consisting of a three-necked flask (500 ml.), a stirrer, a reflux condenser connected to a calcium chloride tube, and a separatory funnel, were introduced granulated zinc (8.8 gm.), a few crystals of iodine, and part of a mixture of diphenylindanone (I) (40 gm.) and ethyl bromoacetate (22.8 gm.) in solution in benzene (60 ml.) and toluene (60 ml.). The flask was carefully heated for a few minutes to start the reaction, which continued without heating by gradually and carefully adding the remainder of the mixture of ketone and acetate. The flask was then heated for three hours. The cooled mixture was slowly poured, with stirring, into one litre of water acidified with sulphuric acid (50 ml.). Two layers were formed. The upper layer was separated by decantation, washed first with water acidified with sulphuric acid and then with distilled water and dried over anhydrous sodium sulphate. The toluene and benzene were distilled off under reduced pressure. The residue crystallized when cooled. It was recrystallized from petroleum ether. Yield, 46 gm. (88%). After another crystallization from ethyl alcohol, the product was almost white; m.p. 93 to 94° C. Ethyl 3-hydroxy-1,1-diphenyl-3-indanacetate is soluble in benzene, toluene, petroleum ether, and methyl and ethyl alcohols. Calc. for $C_{25}H_{24}O_2$: C, 80.64; H, 6.45%. Found: C, 78.54; H, 6.54%.

Ethyl 1,1-Diphenyl-3-indeneacetate (XIII)

A current of dry hydrogen chloride gas was passed through a solution of ethyl 3-hydroxy-1,1-diphenyl-3-indanacetate (10 gm.) in anhydrous toluene (50 ml.). Water droplets soon appeared and after an hour and a half two

layers were formed and the water was easily separated by decantation. The solution in toluene was washed with water and the toluene was distilled off under reduced pressure. The viscous residue was dissolved in methyl alcohol and the solution after having been decolorized with bone black was filtered, concentrated, and cooled. The ethyl 1,1-diphenyl-3-indeneacetate crystallized slowly; m.p. 80 to 81° C. Yield, 6.2 gm. (65%). Ethyl 1,1-diphenyl-3-indeneacetate is soluble in benzene, toluene, methyl, and ethyl alcohols, and acetic acid. A small quantity was dissolved in methyl alcohol and the solution was allowed to evaporate slowly in order to determine whether or not only one of the three possible isomers was present. The crystals obtained from this solution all had the same crystalline form under the microscope and melted at the same temperature, 80 to 81° C. Calc. for $C_{25}H_{22}O$: C, 84.74; H, 6.18%. Found: C, 82.81; H, 6.62%.

1,1-Diphenyl-3-indeneacetic Acid (XIV)

Ethyl 1,1-diphenyl-3-indeneacetate (3 gm.) was treated for half an hour with a boiling solution of potassium hydroxide (5 gm. in 7 ml. of water). The potassium salt formed was dissolved in hot water and the hot solution was filtered with bone black. The decolorized solution was cooled and poured into a large volume of water (500 ml.), acidified with sulphuric acid (10 ml.). The organic acid precipitated. It was filtered off, washed with water, and dried in the oven at 80° C. It was recrystallized once in acetic acid and then in methyl alcohol; m.p. 178 to 179° C. Yield, 21 gm. (76%). Calc. for $C_{23}H_{18}O_2$: C, 84.66; H, 5.52%. Found: C, 82.34; H, 5.59%.

Silver Salt of 1,1-Diphenyl-3-indeneacetic Acid

This silver salt was prepared in the same way as the silver salt of 1,1-diphenyl-3-indanmalonic acid. Calc. for $C_{23}H_{17}O_2Ag$: Ag, 24.92%. Found: Ag, 24.71%.

1,1-Diphenyl-3-indeneacetic Acid p-Nitrobenzyl Ester

This ester was prepared by the method used to obtain the corresponding ester of 1,1-diphenyl-3-indanmalonic acid; m.p. 142 to 143° C. Calc. for $C_{30}H_{23}O_4N$: C, 78.09%; H, 4.99%. Found: C, 78.64%; H, 5.64%.

1,1-Diphenyl-3-indanacetic Acid (VIII)

(a) Prepared from Ethyl 1,1-Diphenyl-3-indeneacetate (XIII)

Ethyl 1,1-diphenyl-3-indeneacetate (3 gm.) was dissolved in glacial acetic acid (30 ml.) and reduced by hydrogen in the presence of platinum oxide (0.4 gm.) as catalyst (2,20), a Parr catalytic reduction apparatus being used. After 30 min., the reaction was complete. The catalyst was filtered off and the solvent distilled. The viscous residue of ethyl 1,1-diphenyl-3-indanacetate (XV) was treated for half an hour with a boiling solution of potassium hydroxide (5 gm. in 7 ml. of water). The potassium salt obtained was dissolved in hot water and the solution was filtered with bone black. The cooled filtrate was slowly poured into a large volume of water (500 ml.) acidified with sulphuric acid (10 ml.). The organic acid precipitated. After standing

it was filtered off, washed with water and dried in the oven at 80° C. Yield: 2.2 gm. (82%). It was recrystallized in methyl alcohol; m.p. 173 to 174° C. It was identified with the monobasic acid previously obtained from 1,1-diphenylindan monobromide by a mixed melting point determination and also by the mixed melting point determination of the derivatives—amide, anilide, and *p*-nitrobenzyl ester.

(b) Prepared from 1,1-Diphenyl-3-indeneacetic Acid (XIV)

1,1-Diphenyl-3-indeneacetic acid (3 gm.) dissolved in glacial acetic acid (30 ml.) was reduced by means of hydrogen in a Parr apparatus in the presence of platinum oxide as catalyst. When the reaction was complete, the catalyst was filtered off, the solvent was distilled off, and the residue crystallized in methyl alcohol; m.p. 173 to 174° C. Yield, 2.5 gm. (84%). The product was identified with the acid previously obtained by a mixed melting point determination.

Acknowledgment

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4-CAMPHORYLTHIOSEMICARBAZIDE AND 4-CAMPHORYLSEMICARBAZIDE[1]

By John A. McRae[2] and William H. Stevens[3]

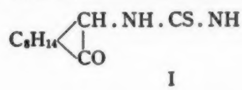
Abstract

4-Camphorylthiosemicarbazide has been prepared by the action of hydrazine hydrate on camphorylthiocarbimide. The analogous semicarbazide has been prepared by a similar reaction. Neither of these substances displays the gel-forming characteristics of 4-camphoryl-2-phenylthiosemicarbazide. From these substances a number of thiosemicarbazones and semicarbazones have been prepared, but although camphoryl-thiosemicarbazide and -semicarbazide are optically active they do not seem to be useful substances for the resolution of racemic aldehydes or ketones. A number of 4-camphoryl-1-(or 2)-arylthiosemicarbazides have been prepared but none displayed the colloidal nature of the 2-phenyl-compound.

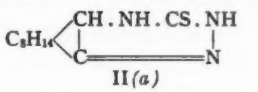
Introduction

The action of phenylhydrazine on camphorylthiocarbimide was observed by Forster and Jackson (4) to produce 1-phenyl- and 2-phenyl-4-camphorylthiosemicarbazide. The substance thought by them to be the latter was obtained in much the larger proportion and was found to have the interesting, although perhaps inconvenient, property of forming gels when dissolved in certain organic solvents. This characteristic property was the subject of a more extended investigation by Hatschek (5) and not long afterwards it was suggested to one of us by Professor (now Sir Martin) Forster that it would be of interest to prepare 4-camphorylthiosemicarbazide (I) and other closely related substances to see if any of such compounds could be found to have the gel-forming power of the 2-phenyl-compound. Camphorylthiosemicarbazide was thereupon prepared and some of its properties studied in Professor Forster's laboratory at the Royal College of Science, but the work was discontinued and not recommenced until recently.

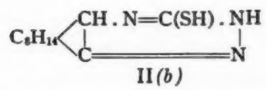
d-4-Camphorylthiosemicarbazide (I) is readily obtained when an alcoholic



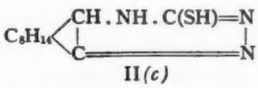
I



II*(a)*



II*(b)*



II*(c)*

solution of camphorylthiocarbimide is added to an ice-cold solution of hydrazine hydrate. This substance is accompanied by small but varying amounts of *sym*-dicamphorylthiocarbamide. Camphorylthiosemicarbazide crystallizes readily and shows no tendency to form gels when dissolved in

[1] *Manuscript received December 1, 1943.*
Contribution from the Chemical Laboratories, Queen's University, Kingston, Ont.
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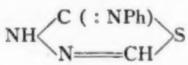
organic solvents. It possesses the reducing powers associated with thiosemicarbazides, easily reducing ammoniacal silver nitrate and Fehling's solution. It unites with aldehydes and ketones and a number of the resulting camphorylthiosemicarbazones have been prepared. In contrast with the parent substances these on the whole do not crystallize well nor are they formed very readily. This substance is apparently the first optically active thiosemicarbazide to have been prepared, but, although it is fully as accessible as the few other optically active bases containing the —NH—NH_2 group that have already been described, it does not seem for the reasons cited that this base will prove useful for the resolution of racemic aldehydes or ketones. For example, it did not give a readily crystallizable derivative with α-ethylhexaldehyde nor with 3-methylcyclohexanone and it does not react with benzoin. By the action of acids the base is readily converted into the anhydride, II(*a*), (*b*), or (*c*). The substance on methylation gives a methyl-derivative in which the methyl group is apparently attached to sulphur, thus pointing to either II(*b*) or II(*c*) as the structure in which it reacts with the methylating agent.

Efforts were made to compare the properties of camphorylthiosemicarbazide with those, on the one hand, of 4-phenylthiosemicarbazide and, on the other, with those of camphoryl-pseudo-semicarbazide prepared by Forster and Fierz (3) by the reduction of N-nitrosocamphoryl-pseudo-carbamide. The ease with which the camphoryl compound forms an anhydride with acids accounts for the differences observed in behaviour from that of the 4-phenyl compound. Thus while the latter yields (7) with formic acid, benzoyl chloride, and acetyl chloride substances of the thiobiazoline type, e.g.,



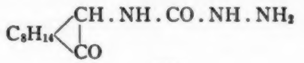
when formic acid is used, the camphoryl compound gives either its anhydride or under very mild conditions its benzoyl and acetyl derivative with the respective reagents.

Forster and Fierz (3) observed that the semicarbazones produced from camphoryl-Ψ-semicarbazide had unusually high rotations, but those prepared from camphorylthiosemicarbazide are devoid of this feature. The Ψ-semicarbazide gave camphoryl azoimide when treated with nitrous acid and was found to react with diazonium compounds and with potassium hypobromite in an interesting manner. Each of these reagents reacts with camphorylthiosemicarbazide but with none of them were conclusive results obtained.

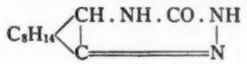
A number of arylcamphorylthiosemicarbazides have been prepared by the action of various arylhydrazines on camphoryl mustard oil. Unlike the results of Forster and Jackson (4) and those of earlier workers on the action of arylhydrazines on mustard oils only one substance was isolated from each reaction, but this was due probably to the much smaller scale on which the present experiments were performed. Using *p*-bromophenylhydrazine the reactants set to a jelly but this quickly disintegrated when purification of the substance was begun. The purified product displayed no gel-forming characteristics

when dissolved in various solvents. It was not possible with the several quantities of these thiosemicarbazides prepared to decide whether the compounds isolated contained the aryl group in the 1- or 2- position. Forster and Jackson described the colour reactions given by the 1-phenyl- and 2-phenyl- compounds with a number of inorganic reagents serving to show sharp differences, but the application of these same reagents gave no clear-cut indication as to whether the arylthiosemicarbazides now described resemble the 1-phenyl or the 2-phenyl-analogue.

4-Camphorylsemicarbazide (III) has been prepared by acting on camphoryl isocyanate with hydrazine hydrate. The isocyanate was prepared according to the directions of Forster and Fierz (2) from Rupe's camphorylthiocarbamide (8). Like its sulphur analogue and like the isomeric pseudo-compound the semicarbazide can be readily converted into an anhydride (IV).



III



IV

With aldehydes and ketones it gives semicarbazones that are not easy to crystallize. These had unexpectedly high melting points, much higher than those of the isomeric pseudo-compounds.

Experimental

4-Camphorylthiosemicarbazide (I)

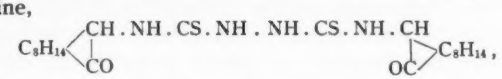
(a) Camphorylthiocarbimide

Isonitrosocamphor (the Claisen mixture prepared in the laboratory from *d*-camphor or purchased from Schuchardt or British Drug Houses) was converted into aminocamphor and thence into camphoryldithiocarbamic acid according to the method of Forster and Jackson (4). This acid after recrystallization was treated either with benzoyl chloride and pyridine or with nitrous acid to produce camphorylthiocarbimide. The latter reagent gave a cleaner product but the yields were inferior to those obtained when benzoyl-chloride–pyridine was used.

(b) Camphorylthiosemicarbazide

Thirty-one grams of recrystallized camphorylthiocarbimide was made into a paste with 185 ml. of alcohol by heating to boiling and cooling rapidly in ice. The ice-cold paste was added gradually in small portions to a cold (0°) solution of 35 gm. of hydrazine hydrate in 70 cc. of water, stirring vigorously and waiting after each addition for the thiocarbimide to react and the product to dissolve. After the mixture had stood for an hour the reaction was complete. A small quantity of material remained undissolved and this was found to be dicamphorylthiourea. M.p. on recrystallization from benzene, 176° C. Calc. for $C_{21}H_{32}O_2N_2S$: N, 7.44%. Found: N, 7.28%. Forster and Jackson describe this substance as having m.p. 176° and as being formed by the action of water or alkali on camphorylthiocarbimide. It was thought

at first that the substance was most likely N-N′-di(camphorylaminothioformyl) hydrazine,



but the analysis and properties of the substance disproved this view.

After the removal of this insoluble material camphorylthiosemicarbazide was precipitated by the addition of water. The collected material after drying was dissolved in hot benzene from which it separated on cooling in fine needles, m.p. 168°*. The yield was 80% of the calculated. $[\alpha]_D + 17.34°$ (c, 0.912 in chloroform). Calc. for $C_{11}H_{19}ON_3S$: N, 17.43; S, 13.27%. Found: N, 17.51; S, 13.38%.

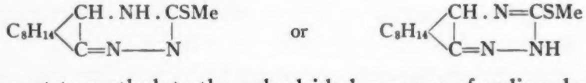
The substance is readily soluble in alcohol, chloroform, and hot benzene. It quickly forms silver sulphide with ammoniacal silver nitrate. Fehling's solution produces a dirty-green precipitate and evolution of nitrogen. When warmed in alcoholic solution with yellow mercuric oxide, mercuric sulphide is formed, accompanied by evolution of nitrogen. On the addition of hydrochloric acid to the thiosemicarbazide it dissolves but the solution gradually deposits the anhydride. Alkali effects a similar transformation. It was converted into the same substance when an attempt was made to prepare its oxime.

Camphorylthiosemicarbazide Anhydride II(a), (b), or (c)

Five grams of camphorylthiosemicarbazide was made into a paste with 50 ml. of water. On the addition of dilute hydrochloric acid the substance dissolved but in a short time it began to deposit crystals; precipitation seemed to be complete after the mixture had stood for two days. The substance deposited was recrystallized from hot alcohol from which it separates in hexagonal plates melting sharply at 239° C. The yield was almost quantitative. $[\alpha]_D + 281.5°$ (c, 0.799 in chloroform). Calc. for $C_{11}H_{17}N_3S$: N, 18.83%. Found: N, 18.96%.

When camphorylthiosemicarbazide was heated with sodium hydroxide the same substance was formed. It was formed also by the action of anhydrous formic acid on the thiosemicarbazide.

Methyl Derivative of Camphorylthiosemicarbazide Anhydride



An attempt to methylate the anhydride by means of sodium hydroxide and dimethyl sulphate gave an oily product having the odour of either methyl mercaptan or dimethyl sulphide.

By adding an alcoholic solution of the anhydride to ammoniacal silver nitrate a yellow silver compound precipitated. This (3 gm.) on drying was heated for 10 hr. with methyl iodide (10 gm.) in dry ether under the reflux.

* *This and all later melting points are corrected.*

Evaporation of the ether after filtration of silver iodide left an oil that gradually solidified. On repeated recrystallization a substance, m.p. 107° C., separating in small prisms was obtained. Calc. for $C_{12}H_{19}N_3S$: N, 17.73%. Found: N, 18.04%. $[\alpha]_D - 57.4°$ (*c*, 0.868 in chloroform).

N-Anilinoformyl-N'-camphorylaminothioformylhydrazine

$$C_8H_{14}\left\langle\begin{array}{l}CH.NH.CS.NH.NH.CONHC_6H_5\\ |\\ CO\end{array}\right.$$

Two grams of camphorylthiosemicarbazide dissolved in 25 ml. chloroform was treated with 1.1 gm. of phenyl isocyanate and allowed to stand 24 hr. in a stoppered bottle. Evaporation of the solvent left a sticky material from which a pure substance was obtained by successive recrystallizations from hot benzene. The material separated with a considerable amount of solvent, which it lost very gradually. M.p. 139° to 143° with decomposition. Calc. for $C_{18}H_{24}O_2N_4S$: N, 15.78%. Found: N, 15.82%. $[\alpha]_D - 63.1°$ (*c*, 0.817 in chloroform).

1-Benzoyl-4-camphorylthiosemicarbazide

$$C_8H_{14}\left\langle\begin{array}{l}CH.NH.CS.NH.NHCOC_6H_5\\ |\\ CO\end{array}\right.$$

Five grams of camphorylthiosemicarbazide and 3 gm. of benzoyl chloride were each dissolved separately in 25 ml. of dry pyridine and the ice-cold solutions mixed. Pyridine hydrochloride gradually separated and after several hours the solution was diluted with water. The material that separated was recrystallized repeatedly from dilute acetone when the benzoyl derivative was obtained, m.p. 225°. Calc. for $C_{18}H_{23}O_2N_3S$: N, 12.18%. Found: N, 12.44%.

A portion of the benzoyl derivative was warmed gently with acetyl chloride. It was recovered unchanged. Marckwald and Bott in a similar experiment with 1-benzoyl-4-phenyl-thiosemicarbazide obtained diphenyliminothiobiazoline.

Condensation of Aldehydes and Ketones with Camphorylthiosemicarbazide

Preparation of Camphorylthiosemicarbazones

The method used was to dissolve separately the aldehyde or ketone and the thiosemicarbazide in a little more than the minimum quantity of hot alcohol. The solutions were mixed and heated on the steam-bath for about an hour. The new derivative separated either on cooling or on dilution with water. The salient data obtained are as follows:

Benzylidene-camphorylthiosemicarbazone. M.p. 215 to 216°. Minute prisms from hot alcohol. $[\alpha]_D + 68.6°$ (*c*, 0.643 in chloroform). Calc. for $C_{18}H_{23}ON_3S$: N, 12.77%. Found: N, 12.73%.

p-Nitrobenzylidene-camphorylthiosemicarbazone. M.p. 234°. Yellow needles from butanol. $[\alpha]_D + 105.2°$ (*c*, 0.842 in chloroform). Calc. for $C_{18}H_{22}O_3N_4S$: N, 14.97%. Found: N, 15.20%.

m-Nitrobenzylidene-camphorylthiosemicarbazone. M.p. 140°. Yellow plates from alcohol. Calc. for $C_{18}H_{22}O_3N_4S$: N, 14.97%. Found: N, 15.20%.

Anisylidene-camphorylthiosemicarbazone. M.p. 148° to 149°. Colourless plates from alcohol. $[\alpha]_D$ + 83.8° (*c*, 0.889 in chloroform). Calc. for $C_{19}H_{25}O_2N_3S$: N, 11.70%. Found: N, 12.15%.

3,4-Diethoxybenzylidene-camphorylthiosemicarbazone. M.p. 111° to 113° from dilute alcohol. $[\alpha]_D$ + 34.6° (*c*, 0.843 in chloroform). Calc. for $C_{22}H_{31}O_3N_3S$: N, 10.31%. Found: N, 10.42%.

Although camphorquinone combines readily with camphoryl-Ψ-semicarbazide it was recovered unchanged when an attempt was made to use it with the thiosemicarbazide. Benzoin failed to react. Cyclohexanone, 3-methylcyclohexanone, and α-ethylhexaldehyde did not give crystalline products. Benzoquinone oxidized the thiosemicarbazide, and formaldehyde gave an ill-defined compound.

1-Aryl-4-camphorylthiosemicarbazides

$$C_8H_{14}\left\langle\begin{array}{l} CH.NH.CS.NH.NHAr \\ | \\ CO \end{array}\right.$$

Combination between camphorylthiocarbimide and arylhydrazines occurs readily. The general practice for the preparation of the following substances was to dissolve separately equimolecular quantities of the reactants in a minimum of hot ethanol or methanol. On mixing, reaction occurred at once and the products were in general easily purified. With *p*-tolylhydrazine and *p*-bromophenylhydrazine the reactants set to gels; this was reminiscent of the behaviour when phenylhydrazine is used but these gels quickly broke up and no difficulty was encountered in obtaining crystalline substances. The substances obtained are all described as 1-aryl-compounds but only with the 1,1-diphenyl-compound is the position of the aryl group a matter of certainty. Forster and Jackson based their structures for the two substances formed when phenylhydrazine is used on the fact that one (the 1-aryl) gave an anhydride, whereas the other did not. Our examination was insufficient to disclose whether any of the substances now prepared forms an anhydride.

1-o-Tolyl-4-camphorylthiosemicarbazide. Colourless plates from alcohol. M.p. 171° C. $[\alpha]_D$ + 34.6 (*c*, 0.820 in chloroform). Calc. for $C_{18}H_{25}ON_3S$: N, 12.69%. Found: N, 13.09.

1-p-Tolyl-4-camphorylthiosemicarbazide. Prismatic crystals from alcohol, in which it is but moderately soluble. M.p. 226° C. $[\alpha]_D$ + 231.6 (*c*, 0.938 in chloroform). Calc. for $C_{18}H_{25}ON_3S$: N, 12.69%. Found: N, 13.74%.

1-m-Nitrophenyl-4-camphorylthiosemicarbazide. Yellow needles from either acetic acid or alcohol. M.p. 204° with decomposition. $[\alpha]_D$ + 313.4 (*c*, 2.934 in chloroform). Calc. for $C_{17}H_{22}O_3N_4S$: N, 15.52%. Found: N, 16.31%. The substance tends to decompose gradually on standing.

1-p-Bromophenyl-4-camphorylthiosemicarbazide. Colourless needles from alcohol. M.p. 227° C. with decomposition. Moderately soluble in hot alcohol.

Difficultly soluble in benzene. $[\alpha]_D + 15.2°$ (*c*, 1.455 in absolute alcohol). Calc. for $C_{17}H_{22}ON_3SBr$: N, 10.66; Br, 20.20%. Found: N, 10.21; Br, 20.05%.

1-(2′,4′-Dinitrophenyl)-4-camphorylthiosemicarbazide. Lemon yellow prisms from butanol. M.p. 218°. The substance was too slightly soluble in chloroform or alcohol for the rotation to be observed accurately. Calc. for $C_{17}H_{21}O_5N_5S$: N, 17.20%. Found: N, 17.01%.

1-β-Naphthyl-4-camphorylthiosemicarbazides. Colourless plates from methanol. M.p. 191°. $[\alpha]_D + 51.1$ (*c*, 3.525 in chloroform). Calc. for $C_{21}H_{25}ON_3S$: N, 11.44%. Found: N, 11.82%.

1,1-Diphenyl-4-camphorylthiosemicarbazide. This substance was made from *as*-diphenylhydrazine and camphorylthiocarbimide. Diphenylhydrazine hydrochloride was treated with caustic soda solution and the free diphenylhydrazine collected in ether. The dried ethereal solution was added to the carbimide also dissolved in ether. Evaporation of the solvent left the crude product, which was repeatedly recrystallized from methanol. Colourless plates. M.p. 223°. $[\alpha]_D - 26.9°$. (*c*, 4.083 in chloroform). Calc. for $C_{23}H_{27}ON_3S$: N, 10.68%. Found: N, 10.62%.

4-Camphorylsemicarbazide (III)

Camphoryl isocyanate was made according to the directions of Forster and Fierz (2). Isonitrosocamphor is reduced to aminocamphor and from the dry ethereal solution of the latter carbon dioxide precipitates its carbonate. This carbonate is then transformed into the normal camphorylcarbamide

$$C_8H_{14}\left\langle \begin{array}{l} CH.NH.CO.NH_2 \\ | \\ CO \end{array} \right.$$

(Rupe (8)) and this when subjected to the action of nitrous acid gives camphorylcarbimide.

An ice-cold solution of 10 gm. of camphoryl isocyanate in 50 ml. of alcohol was added slowly with stirring to 15 gm. of 42% hydrazine hydrate diluted with water to 100 cc. and cooled to 0°. The temperature was maintained at 0° C. during the mixing. On standing 24 hr., camphorylsemicarbazide separated in long needles. It was recrystallized from hot water and on rapid heating melted at 215°. $[\alpha]_D - 26.3$ (*c*, 2.205 in absolute alcohol). Calc. for $C_{11}H_{19}O_2N_3$: C, 58.67; H, 8.44; N, 18.67%. Found: C, 59.50; H, 8.60; N, 18.77%.

The substance reduces ammoniacal silver nitrate, and, like the isomeric pseudo-compound, it is oxidized to camphor by Fehling's solution. It is readily changed by acids into the anhydride. Several semicarbazones were prepared from aromatic aldehydes but with the exception of that made from *p*-nitrobenzaldehyde these were not markedly crystalline. Experiments in which its behaviour towards nitrous acid and diazonium salts was examined failed to give tangible results.

Camphorylsemicarbazide Anhydride (IV)

Camphorylsemicarbazide (1.5 gm.) was dissolved in 25 ml. of dilute hydrochloric acid (1 : 1) and the solution heated gently for several hours. After evaporating off most of the acid the solution was made just alkaline whereupon the anhydride precipitated. The product was recrystallized from hot alcohol and obtained in clusters of fine needles. The substance did not melt below 325° C. but sublimes at about that temperature. $[\alpha]_D + 115.4$ (*c*, 0.658 in absolute alcohol). Calc. for $C_{11}H_{17}ON_3$: C, 63.78; H, 8.28; N, 20.29%. Found: C, 64.06; H, 8.39; N, 20.06%. The substance is soluble in dilute hydrochloric acid, but is unaffected by dilute sodium hydroxide. It does not reduce Tollens' reagent.

m-Nitrobenzylidene-4-camphorylsemicarbazone was prepared from equimolecular quantities of *m*-nitrobenzaldehyde and camphorylsemicarbazide in a manner similar to that in which the thiosemicarbazones already described were prepared. Pale yellow needles. M.p. 178° C. Calc. for $C_{18}H_{22}O_4N_4$: C, 60.33; H, 6.14; N, 15.64%. Found: C, 60.79; H, 6.11; N, 15.74.

p-Nitrobenzylidene-camphorylsemicarbazone. Yellow needles from ethyl alcohol. M.p. 223°. Calc. for $C_{18}H_{22}O_4N_4$: N, 15.64%. Found: 15.80%.

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